Pestic. Sci. 1997, **49**, 313–318

Pharmacokinetics of Intravenous Fenvalerate in Cattle Treated Topically with a Low Dose of Piperonyl Butoxide*

Terry J. Danielson,‡ Lorraine R. Golsteyn & James L. Elder

Research Centre, Agriculture and Agri-Food Canada, PO Box 3000, Lethbridge, Alberta, Canada T1J 4B1.

(Received 29 December 1995; revised version received 3 July 1996; accepted 20 November 1996)

Abstract: Experiments were conducted to identify pharmacokinetic interactions between topically applied piperonyl butoxide and intravenous fenvalerate in cattle (Angus steers). Intact fenvalerate in plasma was derivatized by condensation with acetone and measured by negative chemical ionization gas chromatography/mass spectrometry. Noncompartmental pharmacokinetic analyses indicated that the elimination-phase rate constant (β, 0·000 69 ($\pm$0·000 06) min^{-1}), mean residence time (172 ($\pm$14) min), systemic clearance (10·4 ($\pm$0·7) ml min^{-1} kg^{-1}) or volume at steady state (1800 ($\pm$230) ml kg^{-1}) were not changed ($P > 0·05$) after topical application of a low dose of piperonyl butoxide. These data indicate that topical application of a low dose of the metabolic synergist piperonyl butoxide would not be expected to modify the in-vivo disposition of fenvalerate in cattle.

Key words: fenvalerate, piperonyl butoxide, cattle, insecticide pharmacokinetics

1 INTRODUCTION

Selection pressures due to the use of chemical insecticides can promote emergence of partially resistant strains of insects. This resistance can often be attributed to increased metabolic activities by insect cytochrome P450 (CYP450) enzymes and, in these cases, it may be possible to suppress resistance through simultaneous application of a CYP450 inhibitor such as piperonyl butoxide (PBO).[1–7]

In addition to its effects in insects, PBO also inhibits CYP450 in animals[8,9] and its utilization as a metabolic synergist might also alter the rate of insecticide degradation in non-target food-producing species. We therefore conducted experiments to determine effects of a low dose of topically applied PBO on the pharmacokinetics of fenvalerate, a pyrethroid insecticide, in cattle.

2 EXPERIMENTAL METHODS

2.1 Materials

Fenvalerate (technical grade, Ciba Geigy Canada Ltd) and PBO (80% AI, ICN Pharmaceuticals, Plainview, NY) were employed without further purification. Solvents were HPLC grade.

2.2 Animals procurement and preparation

Three Angus steers (body weights 285 ($\pm$29) kg, range 257–314 kg) were obtained from the Canada Alberta Livestock Research Trust Inc., Lethbridge Alberta. Between experiments, steers were housed in outdoor facilities, with access to enclosed shelter, and were moved to a controlled environment room three days prior to the start of experiments. Approximately 1 h prior to treatment, canulae were inserted into the left and right jugular veins. Solutions of fenvalerate were administered through the left canula. Blood was collected, through the right canula, at 15, 20, 30, 45, 60, 75, 90, 120, 150, 180, 240, 300, 360, 720, 1440 and 2880 min. All collections were timed relative to the start of the infusion. Immediately after collection, blood was centrifuged and plasma was separated and frozen at $-40°C$ until analysis.

Steers first received fenvalerate by intravenous infusion. One month later the same steers were treated topically with PBO and, after 48 h, with fenvalerate, by intravenous infusion. Combined fenvalerate and PBO

* Contribution No. 3879596 from the Lethbridge Research Centre.

‡ To whom correspondence should be addressed.

treatment times were selected to represent exposure to fenvalerate 48 h after placement of an ear tag.

2.3 Dosing procedures

2.3.1 Intravenous infusion with fenvalerate

Solutions of fenvalerate in ethanol + polyethylene glycol-200 (2 + 1 by volume, 45 ml) were filtered (0·45 μm) and infused *via* the left jugular, at a rate of 3 ml min^{-1} during a 15-min infusion period (0·133 mg kg^{-1} min^{-1}, 2 mg kg^{-1}) employing a syringe infusion pump (Harvard Apparatus, Millis Mass).

2.3.2 Topical application of PBO

A solution of PBO in 95% ethanol (10 mg ml^{-1}) was sprayed (PBO, 2 mg kg^{-1}) onto a hair-clipped, rectangular area (100 cm long × body weight in mm wide) centred along the midline of the steer's back. Forty-eight hours later, fenvalerate was infused as described above.

2.4 Analytical techniques

Fenvalerate and its internal standard (flucythrinate) were monitored in plasma by gas chromatography/mass spectrometry (GC/MS) after conversion to esters of 2,2-dimethyl-2-hydroxy-1-(3-phenoxyphenyl)ethanone by condensation with acetone.[10] All analyses were performed in duplicate, according to the following procedure. Internal standard (flucythrinate, 1 μg ml^{-1} in hexane; 50 or 10 μl) was transferred to glass tubes and evaporated. Plasma (1 ml) was then added to each tube, followed immediately by acetone (5 ml). Samples were vortex mixed and allowed to stand at room temperature for 1 h. Acetone-precipitated protein was removed by low-speed centrifugation and aqueous sodium carbonate (100 g $litre^{-1}$; 1 ml) was added to the supernatants. Samples were vortexed and allowed to stand at room temperature overnight. Acetone was then evaporated under nitrogen and the remaining aqueous portions were extracted with hexane (5 ml). Hexane layers were evaporated to dryness under nitrogen and residues were reconstituted in toluene (1 ml). Two-microlitre portions were injected into the gas chromatograph.

Plasma found to contain in excess of approximately 300 ng ml^{-1} fenvalerate was reanalysed either using 0·1 ml portions or after 10 : 1 dilution with fenvalerate-free plasma.

GC/MS was performed using a Hewlett Packard Model 5989A mass spectrometer and a Model 5890, Series 2 gas chromatograph. Analyses were conducted in the negative chemical ionization mode, employing methane as ionization gas. Anions formed through cleavage of ester bonds were monitored by scanning at nominal masses corresponding to $C_{12}H_{13}O_3F_2$ (*m/z* 243, flucythrinate) and $C_{11}H_{12}O_2Cl$ (*m/z* 211 and 213, fenvalerate). Chromatographic separations were achieved on a fused silica column (SPB-1, 19 m, 0·25 mm ID, 0·25 μm film thickness). Helium carrier gas was supplied at a head pressure of 15 psi (104 kPa). Oven temperature was ramped from 100 to 225°C at 30° min^{-1} and then to 290°C at 10° min^{-1}.

2.5 Standard curves

Standard curve samples (1 ml) were prepared in fenvalerate-free plasma to cover two overlapping concentration ranges, 0–10 and 10–500 ng ml^{-1} fenvalerate. Internal standard (flucythrinate) was employed at respective concentrations of 10 or 50 ng ml^{-1}. Amounts of fenvalerate were 1·0, 5·0 and 10·0 ng ml^{-1} or 10·0, 25·0, 50·0, 100·0 and 500·0 ng ml^{-1}.

2.6 Assay validation

On three separate days, quadruplicate series of standard curve samples were prepared from independent stock solutions to contain in 1 ml of plasma 1·0, 5·0 or 10·0 ng and 10·0, 25·0, 50·0, 100 or 500·0 ng of fenvalerate. Flucythrinate (10 or 50 ng) was added, as internal standard, and samples were extracted and analysed as described above.

Intra-assay accuracy and precision were determined by linear regression analysis of the ratios of areas under the GC/MS selected ion responses corresponding to derivatized fenvalerate and flucythrinate. In these experiments, replicate sample set number 1 was employed to generate a standard curve for analysis of replicate sample sets 2–4. Interassay accuracy and precision were determined similarly, by combining results obtained over three days and employing replicate sample sets number 1 for generation of standard curves and replicate sample sets number 2 as validation samples.

2.7 Pharmacokinetic modelling

Plasma concentration/time data were subjected to non-compartmental analyses.[11] Concentrations prior to initiation of infusion ($T = 0$) were assumed to be zero. Elimination-phase rate constants were determined by linear regression analysis of the log transforms of plasma concentrations at 720, 1440 and 2880 min.

Areas under the zero and first moment plasma fenvalerate/time curves were calculated by application of the linear trapezoidal rule (PCNONLIN, Version 4.1. SCI Software, Lexington, KY) and were corrected for areas from the final measurement (2880 min) to infinity by the standard formulae.[11] Mean residence time (MRT, corrected for infusion times), systemic clearance (Cl_s) and volumes at steady-state (V_{ss}) were calculated according to Gibaldi and Perrier.[11]

TABLE 1
Intra-assay Precision and Accuracy

Plasma Concentration (ng ml^{-1})			
Added	*Measured (±S.D.)*[a]	*Precision*[b]	*Accuracy*[c]
1·0	0·84 (±0·04)	5·0	84·0
5·0	4·5 (±0·4)	8·8	90·0
10·0	9·4 (±0·7)	7·4	94·0
25·0	24·4 (±1·2)	4·9	97·5
50·0	50·0 (±3·6)	7·2	100·0
100·0	101·1 (±9·5)	9·4	101·1
500·0	464 (±29)	6·3	92·8

[a] $N = 3$.
[b] S.D./mean × 100.
[c] Measured/added × 100.

Data are reported as arithmetic means and standard deviations, except for elimination $T\frac{1}{2\beta}$ where harmonic means are reported.

2.8 Statistical analysis

Values of parameters describing the pharmacokinetics of fenvalerate in plasma from cattle treated either with fenvalerate or fenvalerate plus PBO were compared by a paired Student's T test (GraphPad Instat, V 2.0, GraphPad Software). Statistical significance was set at $P < 0{\cdot}05$.

TABLE 2
Inter-assay Precision and Accuracy

Plasma concentration (ng ml^{-1})			
Added	*Measured (±S.D.)*[a]	*Precision*[b]	*Accuracy*[c]
1·0	1·0 (±0·5)	50·0	100·0
5·0	6·5 (±1·3)	20·0	130·0
10·0	9·6 (±0·7)	7·3	96·0
25·0	26·4 (±2·6)	9·8	105·6
50·0	49·1 (±4·2)	8·5	98·2
100·0	97·6 (±5·4)	5·6	97·6
500·0	462 (±43)	9·3	92·4

[a] $N = 3$.
[b] S.D./mean × 100.
[c] Measured/added × 100.

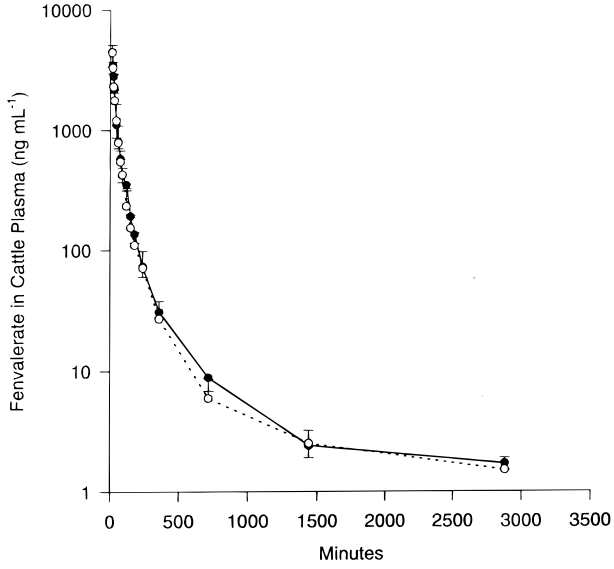

Fig. 1. Semilogarithmic plot of fenvalerate concentration in cattle plasma against time (—● —) after treatment by intravenous infusion with fenvalerate (2 mg kg^{-1}) alone and (— ○ —) 48 h after topical application of PBO (2 mg kg^{-1}) ($N = 3$, means ±S.D.).

3 RESULTS

Pyrethroid insecticides produce well-defined symptoms originating from within the central nervous systems of treated animals.[12–16] Steers receiving fenvalerate by intravenous infusion at the dose employed in our experiments (2 mg kg^{-1}) exhibited characteristic signs of pyrethroid toxicity which persisted for approximately 1 h after dosing. Symptoms included drooped ears and lowered head position, increased salivation and a rhythmic side-to-side swaying motion.

Linearity and accuracy of the mass spectral analyses were studied by spiking 1 ml plasma samples with fenvalerate of concentrations from 1 to 500 ng ml^{-1}. Weighting factors were not applied. Estimates of intra-

TABLE 3
Pharmacokinetics of Intravenous Fenvalerate in Angus Steers[a]

		Animal number			
Parameter	*Units*	*700*	*793*	*842*	*Mean (±S.D.)*
Beta	min^{-1}	0·000 62	0·000 72	0·000 73	0·000 69 (±0·000 06)
$T\frac{1}{2\beta}$	min	1118	962	950	1005[b]
MRT	min	168	188	160	172 (±14)
Cl_s	ml min^{-1} kg^{-1}	10·6	10·9	9·6	10·4 (±0·7)
V_{ss}	ml kg^{-1}	1780	2050	1540	1800 (±260)

[a] 2·0 mg kg^{-1} infused over 15 min; abbreviations as in materials and methods.
[b] Harmonic mean.

TABLE 4
Pharmacokinetics of Intravenous Fenvalerate in Angus Steers following Topical Application of Piperonyl Butoxide[a]

Parameter	Units	Animal number			Mean (±S.D.)
		700	793	842	
Beta	min^{-1}	0·000 62	0·000 70	0·000 46	0·000 59 (±0·000 12)
$T\frac{1}{2\beta}$	min	1120	990	1506	1174[b]
MRT	min	125	183	242	185 (±80)
Cl_s	ml min^{-1} kg^{-1}	10·1	10·3	14·7	11·7 (±2·6)
V_{ss}	ml kg^{-1}	1255	1885	3560	2230 (±1190)

[a] 2·0 mg kg^{-1} fenvalerate infused over 15 min, PBO topical 2 mg kg^{-1} 48 h prior.
[b] Harmonic mean.

and interassay variability are shown in Tables 1 and 2. Based on these data, the limit of quantization of fenvalerate in plasma was set at 1 ng ml^{-1}.

Concentration/time plots of fenvalerate in plasma are illustrated in Fig. 1. These plots are characterized by initial rapidly declining levels of fenvalerate followed by more prolonged terminal elimination phases of approximately 16 to 18 h. Pharmacokinetic parameters calculated from these data are shown in Tables 3 and 4. Statistically significant differences ($P < 0·05$) were not observed between any parameter data sets. In each case, mean values of Cl_s and V_{ss} of fenvalerate were near 10 ml min^{-1} kg^{-1} and 2000 ml kg^{-1}, respectively.

4 DISCUSSION

Pyrethroid insecticides are in general thought to undergo rapid metabolic degradation *in vivo* and to present little risk to consumers of products derived from exposed animals. Small amounts of pyrethroid can, however, persist in fatty tissues of food-producing animals for extended periods of time. For example, Boyer *et al.*[17] reported that fatty tissues collected from cattle 20 days after exposure retained small amounts of unchanged fenvalerate. Similarly, Quistad *et al.*[18] estimated that, eight days after oral treatment of cattle with fluvalinate, approximately 1·6% of the total dose remained in fat. Small amounts of various pyrethroids have also been detected in milk after oral or topical treatment of dairy cattle.[19,20] In each of these examples, the residue was unchanged pyrethroid. Our experiments were therefore conducted to investigate whether exposure to a metabolic synergist, like PBO, might alter fenvalerate elimination by cattle and indirectly increase the amount available for accumulation into fatty tissue.

Application of PBO to the skin of cattle did not alter the pharmacokinetics, in plasma, of subsequently infused fenvalerate. This conclusion is straightforward since concentration/time curves of fenvalerate (Fig. 1), with or without PBO pretreatment, were virtually superimposable. Similarly, statistically significant changes in the magnitudes of derived pharmacokinetic parameters were not observed after application of PBO (Tables 3 and 4). In somewhat similar experiments, Marti-Mestres *et al.*[21,22] demonstrated that maintenance of swine or chickens on diets adulterated with the pyrethroid deltamethrin and PBO, each at the maximum residue limits, also did not result in detectable accumulation of residue in target organs.

Several cautionary points should be applied to this interpretation of the data. Fenvalerate is commonly applied to cattle from eartags and the dose of it and of PBO (2 mg kg^{-1}) employed in our experiments was selected to approximate 50% release from a single eartag impregnated at 10% with each ingredient. This amount of PBO is small in comparison to doses employed during enzyme regulation studies[1,2] and may be further reduced by slow or incomplete percutaneous absorption.[23] Effects of PBO on enzyme activities are also often multiphasic, with initial inhibition being replaced by induction,[24] and the response prevailing in cattle 48 h after treatment has not been determined. However, in order to provide adequate time for PBO absorption, and yet reflect de-novo release of pyrethroid from an eartag, PBO was applied on to the skin 48 h prior to administration of fenvalerate. Our data therefore do not indicate that metabolism of fenvalerate by cattle is insensitive to PBO but only that topical application of a low dose could not be demonstrated to modify the elimination of intravenously infused pyrethroid.

The data allow some general observations regarding the pharmacokinetics of fenvalerate in cattle. Fenvalerate concentration in cattle plasma decreased in a clearly multiphasic pattern with an approximately 5 : 1 ratio between $T\frac{1}{2\beta}$ and MRT. This relatively high ratio suggests that a significant portion of the dose was eliminated from plasma, possibly by metabolism, prior to emergence of a terminal elimination phase. Metabolic clearance of fenvalerate therefore appears to be rapid and its relatively long terminal-phase half-life in cattle plasma may reflect slow release of unchanged pyrethroid previously distributed into fatty tissue. This

interpretation is consistent with previous observations in sheep[25] and also with reports that small amounts of unchanged pyrethroid can persist for several weeks in fatty tissues of treated animals.[17–20,26–28]

The data also indicate a possible species dependency in the pharmacokinetics of fenvalerate. In cattle, Cl_s of fenvalerate was near 10 ml min^{-1} kg^{-1}, equivalent to approximately one-third of hepatic flow and 15% cardiac output. This is similar to the rate of 15 ml min^{-1} kg^{-1} calculated from blood data collected after treatment of rats by intravenous injection with a low dose of deltamethrin (1·75 mg kg^{-1}).[12] In comparison, Cl_s of fenvalerate in sheep was previously reported to be near 50 ml min^{-1} kg^{-1} which is in excess of hepatic plasma flow and equivalent to approximately 70% of cardiac output.[25] Similar species differences have been reported regarding the pharmacokinetics of lidocaine, where rates of clearance in excess of hepatic plasma flow have been attributed to more efficient hepatic extraction plus irreversible extrahepatic mechanisms.[29–32] This possible explanation suggests that extrahepatic mechanisms may contribute less to elimination of fenvalerate by cattle than by sheep.

We have reported previously that administration of fenvalerate to sheep by short intravenous infusion resulted in a reduced toxic response in comparison to an intravenous injection.[25] Steers were therefore also treated by short intravenous infusion. In cattle, as in sheep, symptoms began approximately 10 min after initiation of the infusion and continued for 30–45 min.

Gray and Rickard[13,14,27] observed that the threshold level for deltamethrin in CNS to produce writhing in mice and rats was near 500 ng g^{-1}. Fenvelerate in cattle plasma exceeded this level until 90 min after treatment (Fig. 1) and approached the assay's limit of quantitation (1 ng ml^{-1}) during the terminal elimination phase. Reductions in dose adequate to reduce initial concentrations below the pharmacological threshold may also require an equivalent enhancement of assay sensitivity in order to detect fenvalerate during the elimination phase.

It has previously been reported that pyrethroids administered by intravenous injection can precipitate from blood and deposit into the first encountered capillary bed. This has been shown, in rodents treated with high doses of bioresmethrin (300–500 mg kg^{-1}),[14] to result in delayed entry into the brain and delayed development of toxic signs. In contrast, after smaller doses (1·75 mg kg^{-1}) of deltamethrin,[12] levels in nervous tissue parallelled levels in blood and toxicity developed over the same time-frame as after intracerebral administration.[15,16] Precipitation from blood may therefore be a function of dose and might not occur after treatments with the low dose of fenvalerate employed in our experiments.

Administration of fenvalerate by intravenous infusion has allowed us to address the pharmacokinetics and pharmacodynamics of this lipophilic substance in cattle. Our data do not indicate a pharmacokinetic interaction between intravenous fenvalerate and a low dose of topically applied PBO and suggest that incorporation of PBO into insecticidal eartags would not be expected to significantly modify the pharmacokinetics of fenvalerate in cattle.

ACKNOWLEDGEMENT

The authors wish to thank the Canada Alberta Livestock Research Trust for provision and maintenance of test animals.

REFERENCES

1. Macdonald, R. S., Solomon, K. S., Surgeoner, G. A. & Harris, C. R., Laboratory studies on the mechanisms of resistance to permethrin in a field-selected strain of house flies. *Pestic. Sci.*, **16** (1985) 10–16.
2. Wheelock, G. D. & Scott, J. G., Immunological detection of cytochrome P450 from insecticide resistant and susceptible house flies (*Musca domestica*). *Pestic. Biochem. Physiol.*, **38** (1990) 130–9.
3. Wheelock, G. D. & Scott, J. G., The role of cytochrome $P450_{lpr}$ in deltamethrin metabolism by pyrethroid resistant and susceptible strains of house flies. *Pestic. Biochem. Physiol.*, **43** (1992) 67–77.
4. Bull, D. L. & Pryor, N. W., *In vivo* and *in vitro* fate of fenvalerate in house flies. *Pestic. Biochem. Physiol.*, **38** (1990) 140–52.
5. Scott, J. G. & Georghiou, G. P., Mechanisms responsible for high levels of permethrin resistance in the house fly. *Pestic. Sci.*, **17** (1986) 195–206.
6. Funaki, E., Dauterman, W. C. & Motoyama, N., *In vitro* and *in vivo* metabolism of fenvalerate in pyrethroid resistant house flies. *Nihon Noyaku Gakkaishi* (*J. Pestic. Sci.*), **19** (1994) 43–52.
7. Golenda, C. F. & Forgash, A. J., The distribution and metabolism of fenvalerate in pyrethroid-resistant and susceptible house flies. *Pestic. Biochem. Physiol.*, **33** (1989) 37–48.
8. Adams, N. H., Levi, P. E. & Hodgson, E., Regulation of cytochrome P-450 isozymes by methylenedioxyphenyl compounds. *Chem.-Biol. Interactions*, **86** (1993) 255–74.
9. Adams, N. H., Levi, P. E. & Hodgson, E., Differences in induction of three P450 isozymes by piperonyl butoxide, sesamex, safrole and isosafrole. *Pestic. Biochem. Physiol.*, **46** (1993) 15–26.
10. Saleh, M. A., Marei, A. E-S. & Casida, J. E., α-Cyano-3-phenoxybenzyl pyrethroids: Derivatizations at the benzylic position. *J. Agric. Food Chem.*, **28** (1980) 592–4.
11. Gibaldi, M. & Perrier, D., *Pharmacokinetics*, 2nd edn. Marcel Dekker Inc., New York and Basel, 1982.
12. Gray, A. J. & Rickard, J., The toxicokinetics of deltamethrin in rats after intravenous administration of a toxic dose. *Pestic. Biochem. Physiol.*, **18** (1982) 205–15.
13. Gray, A. J. & Rickard, J., Toxicity of pyrethroids to rats after direct injection into the central nervous system. *Neurotoxicology*, **3** (1982) 25–35.
14. Gray, A. J., Connors, T. A., Hoellinger, H. & Nam, N-H., The relationship between the pharmacokinetics of intravenous cismethrin and bioresmethrin and their mammalian toxicity. *Pestic. Biochem. Physiol.*, **13** (1982) 281–93.

15 Lawrence, L. J. & Casida, J. E., Pyrethroid toxicology: Mouse intracerebral structure–activity relationships. *Pestic. Biochem. Physiol.*, **18** (1982) 9–14.
16. Staatz, C. G., Bloom, A. S. & Lech, J. J., A pharmacological study of pyrethroid neurotoxicology in mice. *Pestic. Biochem. Physiol.*, **17** (1982) 287–92.
17. Boyer, A. C., Lee, P. W., & Potter, J. C., Characterization of fenvalerate residues in dairy cattle and poultry. *J. Agric. Food Chem.*, **40** (1992) 914–18.
18. Quistad, G. B., Staiger, L. E., Jamieson, G. C. & Schooley, D. A., Metabolism of fluvalinate by a lactating dairy cow. *J. Agric. Food Chem.*, **30** (1982) 895–901.
19. Frank, R., Braun, H. E., Miller, L. A. & Allan, G. W., Fenvalerate residues in milk following topical treatments to dairy cows. *Pestic. Sci.*, **15** (1984) 600–4.
20. Wszolek, P. C., Lein, D. H. & Lisk, D. J., Excretion of fenvalerate insecticide in the milk of dairy cows. *Bull. Environ. Contam. Toxicol.*, **24** (1980) 296–8.
21. Marti-Mestres, G. N., Cooper, J-F. M., Mestres, J-P. M., De Wilde, G. & Wynn, N. R., Effects of a supplemented deltamethrin and piperonyl butoxide diet on residues in products of animal origin. 1. Feeding study in pigs. *J. Agric. Food Chem.*, **41** (1993) 2416–20.
22. Marti-Mestres, G. N., Cooper, J-F. M., Mestres, J-P. M., De Wilde, G. & Wynn, N. R., Effects of a supplemented deltamethrin and piperonyl butoxide diet on levels of residues in products of animal origin. 2. Feeding study in poultry. *J. Agric. Food Chem.*, **43** (1995) 1039–43.
23. Wester, R. C., Bucks, D. A. W. & Maibach, H. I., Human *in vivo* absorption of pyrethrin and piperonyl butoxide. *Food Chem. Toxicol.*, **32** (1994) 51–3.
24. Kamienski, F. X. & Murphy, S. D., Biphasic effects of methylenedioxyphenyl synergists on the action of hexobarbital and organophosphate insecticides in mice. *Toxicol. Appl. Pharmacol.*, **18** (1971) 883–94.
25. Danielson, T. J., Golsteyn, L. R. & Elder, J. L., Pharmacokinetics of intravenous fenvalerate in sheep. *Pestic. Sci.*, **46** (1996). 145–50.
26. Marei, A. E-S., Ruzo, L. O. & Casida, J. E., Analysis and persistence of permethrin, cypermethrin, deltamethrin and fenvalerate in the fat and brain of treated rats. *J. Agric Food Chem.*, **30** (1982) 558–62.
27. Gray, A. J. & Rickard, J., Distribution of radiolabel in rats after intravenous injection of a toxic dose of ^{14}C-acid, ^{14}C-alcohol or ^{14}C-cyano-labeled deltamethrin, *Pestic. Biochem. Physiol.*, **16** (1981) 79–85.
28. Mandal, T. K., Bhattacharya, A., Chakraborty, A. K. & Basak, D. K., Disposition kinetics, cytotoxicity and residues of fenvalerate in tissue following oral administration to goats. *Pestic. Sci.*, **35** (1992) 201–7.
29. Engelking, L. R., Lofstedt, J., Blyden, G. T. & Greenblatt, D. J., Antipyrine and lidocaine are cleared faster in horses than in humans: acetaminophen may be handled similarly. *Pharmacol.*, **34** (1987) 192–200.
30. Branch, R. A., Shand, D. G., Wilkinson, G. R. & Nies, A. S., The reduction of lidocaine clearance by *dl*-propranolol: an example of hemodynamic drug interaction. *J. Pharmacol. Exp. Ther.*, **184** (1973) 515–19.
31. Lautt, W. W. & Skelton, F. S., The effect of SKF-525A and of altered hepatic blood flow on lidocaine clearance in the cat. *Can. J. Physiol. Pharmacol.*, **55** (1976) 7–12.
32. Engelking, L. R., Blyden, G. T., Lofstedt, J. & Greenblatt, D. G., Pharmacokinetics of antipyrine, acetaminophen and lidocaine in fed and fasted horses. *J. Vet Pharmacol. Therap.*, **10** (1987) 73–82.